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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,932	04/05/2004	Jonathan Schneck	001107.00466	7013

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/816,932	SCHNECK ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-23 and 53-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-23 and 53-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 3/29/06 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election of Group I (claims 21-23 and newly added claims 53-56), and species of dendritic cell, chimeric protein comprising an HLA-A2 MHC class I molecule and an IgG1 heavy chain comprising a variable region, and the HTLV-1 tax 11-19 peptide in Applicant's response filed 11/2/05.

Claims 21-23 and 53-56 read on the elected species and are currently being examined.

3. The amendment filed 4/5/04 stands objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the incorporation by reference to application serial nos. 09/789,720 and 09/150,622.

Applicant is required to cancel the new matter in the reply to this Office Action.

Applicant's argument has been fully considered, but is not persuasive.

Applicant's position on page 6 of Applicant's said amendment filed 3/29/06 is that the instant specification is a divisional application of parent application serial no 09/789,720 which in turn is a divisional of serial no. 09/150,622.

It is the Examiner's position that although the instant application is a divisional application, Applicant is incorporating by reference to all non-provisional and provisional parent applications, and Applicant may not incorporate by reference the said parent applications after the filing date unless the amendment to incorporate by reference is in a preliminary amendment that is mentioned in the oath or declaration.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 21-23 and 53-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not supported by the instant specification and claims as originally filed is as follows: "at least two chimeric proteins are bound to the surface of the cell, wherein each chimeric protein comprises an MHC molecule and an immunoglobulin chain; wherein the at least two chimeric proteins associate to form a molecular complex." The originally filed disclosure is to a composition comprising a cell in which a chimeric protein is bound to the surface of the cell, wherein the chimeric protein comprises an MHC molecule and an immunoglobulin chain; wherein the chimeric protein associates to form a molecular complex.

6. Applicant is requested to clarify the amendment of the brief description of the drawings for Figure 1B, *i.e.,* SEQ ID NO: 6 and SEQ ID NO: 7 appear to be sequences appearing in the said figure that flank the (α1-α3) regions, but the way the description has been amended, the said SEQ ID NO appear to describe the (α1-α3) regions.

7. For the purpose of prior art rejections, the filing date of the instant claims 21-23 and 53-56 is deemed to be the filing date of the instant application, *i.e.,* 4/5/04, as per paragraph #5 supra of this Office Action.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 21-23 and 53 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/03552 A2 (1/29/98) in view of Celluzzi *et al* (J. Exp. Med. 1/1996, Vol. 183, pages 283-287), Liu *et al* (J.Exp. Med. 1/1997, Vol. 185, No. 1, pages 165-170) and Bendig (Methods: A Companion to Methods in Enzymology, 1995, Vol. 8, pages 83-93).

WO 98/03552 A2 teaches multivalent MHC complex/peptide/IgG fusion proteins, *i.e.,* chimeric proteins, such proteins comprising at least two MHC class I HLA-A molecules attached to a linker, or MHC class II molecules, the linker being IgG1 and each MHC class I molecule bound or fused to an identical peptide. WO 98/03552 A2 further teaches that the linker determines whether the fusion protein will activate or suppress T cells. WO 98/03552 A2 teaches that for enhancing T cell-mediated immunity, the linker will allow delivery of a second, or co-stimulatory signal, this being accomplished by using an IgG that has binding affinity for a cell surface structure on a cell that is capable of delivering a co-stimulatory signal. WO 98/03552 A2 teaches *in vitro* stimulation of T cells using immobilized fusion protein (especially Background and Summary of the Invention, Brief Description of the Drawings for Figure 1, last paragraph on page 2, first two paragraphs on page 3, page 4 at lines 25-26, Figure 1, claims 1-3, 8, 20-23).

WO 98/03552 A2 does not teach wherein the the fusion (or chimeric) protein is bound to a cell, nor wherein the cell is a dendritic cell, nor wherein the cell capable of delivering a co-stimulatory signal is a dendritic cell.

Celluzzi *et al* teach that priming of CTL responses requires the presentation of the relevant antigen by professional antigen presenting cells (APCs) capable of providing co-stimulation, that dendritic cells (DC) are efficient APCs for CTL induction, and that dendritic cells may therefore be an attractive adjuvant for immunizations. Celluzzi *et al* teach that DC pulsed with antigen induce CTL-mediated response to the said antigen (especially first paragraph on page 283), and that such DC is advantageous over other forms of peptide delivery in that the peptide in preformed complexes with class I on the surface of the DC is likely to be presented in the appropriate APC context for T cell stimulation, and that the peptide will be protected from degradation by extracellular proteases (especially last sentence in column 1 on page 286). Celluzzi *et al* teach cell surface antigens on DC, and detection of cell surface antigens using antibodies specific for said cell surface antigens (especially Preparation of DC section at column 2 on page 283).

Liu *et al* teach an IgG1 isotype mouse monoclonal antibody 7D6 specific for the human dendritic cell marker CD21 (especially abstract and Materials and Methods section on page 166 at the second and third full paragraphs at column 1).

Bendig teaches that rodent antibodies may be humanized to avoid adverse immune reactions to rodent sequences when used therapeutically (see entire article).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an MHC class I/peptide/IgG1 fusion protein as taught by WO 98/03552 A2 using a humanized version as taught by Bendig of an IgG1 antibody comprising a variable region specific for a DC cell surface antigen such as taught by Celluzzi *et al* and by Liu *et al*, and to have attached the fusion protein to a cell capable of delivering a co-stimulatory signal as taught by WO 98/03552 A2, said cell being a DC taught by Celluzzi *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prepare a composition comprising said fusion protein attached to a cell capable of providing a co-stimulatory signal as taught by WO 98/03552 A2 because Celluzzi *et al* teach that DC are capable of providing the requisite co-stimulatory signal, and further teach the advantage of using DC with peptide bound to MHC on their surface for immunization, Liu et al teach a mouse IgG1 antibody to a dendritic cell marker, and Bendig teach humanization of rodent antibodies when used therapeutically in humans. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this because Celluzzi *et al* teach that the peptide is likely to be protected from degradation from extracellular

proteases while bound to class I, and the construct taught by WO 98/03552 A2 has peptides that are either bound or fused to class I MHC.

With regard to the limitation "at least two chimeric proteins are bound to the surface of the cell," and "wherein the at least two chimeric proteins associate to form a molecular complex," the instant claims are included in this rejection because the multivalent complexes comprise more than one chimeric protein.

10. Claims 21-23 and 53-56 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/03552 A2 (1/29/98) in view of Celluzzi *et al* (J. Exp. Med. 1/1996, vol. 183, pages 283-287), Liu *et al* (J.Exp. Med. 1/1997, Vol. 185, No. 1, pages 165-170) and Utz *et al* (J. Virology, 2/1996, Vol. 70, No. 2, pages 843-851).

WO 98/03552 A2 teaches multivalent MHC complex/peptide/IgG fusion proteins, *i.e.,* chimeric proteins, such proteins comprising at least two MHC class I HLA-A molecules attached to a linker, or MHC class II molecules, the linker being IgG1 and each MHC class I molecule bound or fused to an identical peptide. WO 98/03552 A2 further teaches that the linker determines whether the fusion protein will activate or suppress T cells. WO 98/03552 A2 teaches that for enhancing T cell-mediated immunity, the linker will allow delivery of a second, or co-stimulatory signal, this being accomplished by using an IgG that has binding affinity for a cell surface structure on a cell that is capable of delivering a co-stimulatory signal. WO 98/03552 A2 teaches *in vitro* stimulation of T cells using immobilized fusion protein (especially Background and Summary of the Invention, Brief Description of the Drawings for Figure 1, last paragraph on page 2, first two paragraphs on page 3, page 4 at lines 25-26, Figure 1, claims 1-3, 8, 20-23).

WO 98/03552 A2 does not teach wherein the the fusion (or chimeric) protein is bound to a cell, nor wherein the cell is a dendritic cell, nor wherein the cell capable of delivering a co-stimulatory signal is a dendritic cell, nor wherein the MHC molecule is HLA-A2, nor wherein the antigenic peptide is HTLV-1 tax 11-19.

Celluzzi *et al* teach that priming of CTL responses requires the presentation of the relevant antigen by professional antigen presenting cells (APCs) capable of providing co-stimulation, that dendritic cells (DC) are efficient APCs for CTL induction, and that dendritic cells may therefore be an attractive adjuvant for immunizations. Celluzzi *et al* teach that DC pulsed with antigen induce CTL-mediated response to the said antigen (especially first paragraph on page 283), and that such DC is advantageous over other forms of peptide delivery in that the peptide in preformed complexes with class I on the surface of the DC is likely to be presented in the appropriate APC context for T cell stimulation, and that the peptide will be protected from degradation by extracellular proteases (especially last sentence in column 1 on page 286). Celluzzi *et al* teach cell surface antigens on DC, and detection of cell surface antigens using antibodies specific for said cell surface antigens (especially Preparation of DC section at column 2 on page 283).

Liu *et al* teach an IgG1 isotype mouse monoclonal antibody 7D6 specific for the human dendritic cell marker CD21 (especially abstract and Materials and Methods section on page 166 at the second and third full paragraphs at column 1).

Utz et al teach in HLA-A2 positive individuals with HTLV-1 associated HAM/TSP, the vast majority of CD8+ HTLV-1 specific CTL recognize one viral epitope presented by HLA-A2, the immunodominant HTLV-1 tax 11-19 peptide (especially abstract and introduction sections). *Utz et al* teach detecting the presence of such CD8+ T cells using target cells transfected with HLA-A2 and pulsed with the tax 11-19 peptide (especially first section at column 1 on page 8450. *Utz et al* teach that it is not known if the virus-specific CTL are beneficial to the patient or contribute to the pathogenesis of the condition (especially second to last paragraph of article on page 850). *Utz et al* teach generation of the CTL by stimulating CD8+ cells from peripheral blood of patients with antigen pulsed PBL (Materials and Methods section, last paragraph, column 1 on page 844).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an MHC class I/peptide/IgG fusion protein as taught by WO 98/03552 A2 using an IgG1 antibody comprising a variable region specific for a DC cell surface antigen such as taught by Liu *et al*, and to have attached the fusion protein to a cell capable of delivering a co-stimulatory signal as taught by WO 98/03552 A2, said cell being a DC taught by Celluzzi *et al*. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an MHC class I/viral peptide/IgG1 fusion protein using the tax 11-19 peptide and HLA-A2 taught by Utz *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prepare a composition comprising said fusion protein attached to a cell capable of providing a co-stimulatory signal as taught by WO 98/03552 A2 because Celluzzi *et al* teach that DC are capable of providing the requisite co-stimulatory signal, and further teach the advantage of using DC with peptide bound to MHC on their surface for immunization, Liu et al teach a mouse IgG1 antibody to a dendritic cell marker. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this because Celluzzi *et al* teach that the peptide is likely to be protected from degradation from extracellular proteases while bound to class I, and the construct taught by WO 98/03552 A2 has peptides that are either bound or fused to class I MHC. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prepare a standardized, stable source of APC that provide a strong co-stimulatory signal along with the tax 11-19 peptide bound to HLA-A2 because Utz *et al* teach generation of tax 11-19/HLA-A2 specific CTL from peripheral blood of HTLV-1 patients with HAM/TSP using PBL isolated from HLA-A2 positive patients and pulsed with tax 11-19 immunodominant peptide. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to stimulate and expand CTL

in vitro for further study since Utz *et al* teach that it is not known if virus-specific CTL are beneficial or deleterious, and the combined references teach *in vitro* stimulation of T cells using immobilized fusion protein.

With regard to the limitation "at least two chimeric proteins are bound to the surface of the cell," and "wherein the at least two chimeric proteins associate to form a molecular complex," the instant claims are included in this rejection because the multivalent complexes comprise more than one chimeric protein.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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